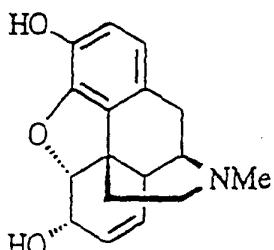


## PROCESS FOR PREPARATION OF 4,5-EPOXYMORPHINAN-6-OXYGLUCURONIDES

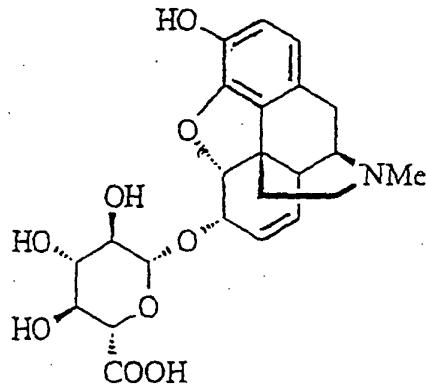
### BACKGROUND OF THE INVENTION

According to recent publications the morphine metabolite Morphine-6- $\beta$ -D-glucuronide (M6G) [ 6 ] is a more effective and longer lasting analgesic drug than Morphine [ 5 ] with fewer side effects<sup>1</sup> and, therefore, there is much interest in using M6G, rather than Morphine, as a pain killing drug.<sup>2</sup>



Morphine

[ 5 ]



Morphine-6- $\beta$ -D-glucuronide (M6G)

[ 6 ]

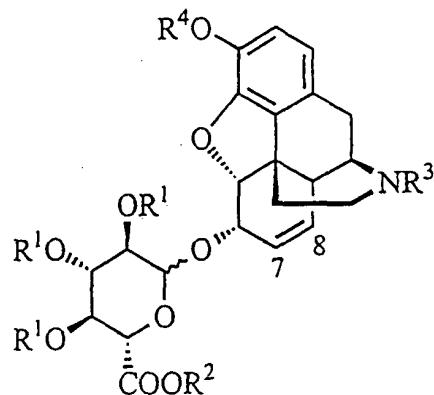
The traditional approach to glycosylation of 4,5-Epoxy morphinan-6-ols explores Bromoglucuronides as glycoside donor and the Koenings-Knorr procedure for the activation of Bromoglucuronides (Berrang, B., et al., Synthesis, 1997, p. 1165 and references cited therein).

Another approach (Scheinmann, F. et. al., US Pat. No. 5621087, see Claim 1, 2, 5 and 6, abstract, examples, column 4, line 25 - line 45)

explores the use of Lewis acids (of the type  $\text{BF}_3$  and  $\text{TMSOTf}$ ) rather than heavy metals based Lewis acids (March, J., "Advanced Organic Chemistry", 4-th edition, A Whiley-Interscience publication, pp. 260-3) for the activation of Bromoglucuronides.

Unfortunately, we did not succeed to obtain 4,5-Epoxy morphinan-6-ols from Bromoglucuronides using activators proposed in US Pat. No. 5621087 and did not find such examples in the literature.

Unexpectedly we found that the O-glycosylation of 4,5-Epoxy morphinan-6-ols with Bromoglucuronides was accelerated by Zinc containing compounds to give 4,5-Epoxy morphinan-6-oxyglucuronides of formula [1] with high yield.



[1]

wherein:

position 7 and 8 can be olefin as shown or dihydro adduct;  
 $\text{R}^1$  are alkyl, haloalkyl, arylmethyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, haloalkoxycarbonyl, vinyloxycarbonyl or allyloxycarbonyl,

R<sup>2</sup> is alkyl, haloalkyl or aralkyl;

R<sup>3</sup> is alkyl, arylmethyl, allyl, cyclopropylmethyl, cyclobutylmethyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, haloalkoxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl or hydrogen;

R<sup>4</sup> is alkyl, haloalkyl, arylmethyl, 2-(4-morpholinyl)ethyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, haloalkoxycarbonyl, vinyloxycarbonyl or allyloxycarbonyl.

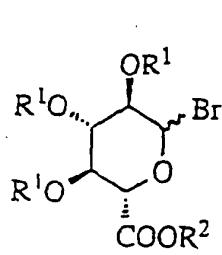
We also found that the  $\alpha$  and  $\beta$  anomeric selectivity of the conjugation product can be controlled by using different O-protecting groups in aglycon and in Bromoglucuronide as well as by varying the ratio between 4,5-Epoxymorphinan-6-ols and Zinc containing compounds.

It is important to note that only the  $\beta$ -anomer of 4,5-Epoxymorphinan-6-oxyglucuronides was obtained according to Koenings-Knorr procedure and US Patent No. 5621077 procedure (but with another then Bromoglucuronide glycoside donor).

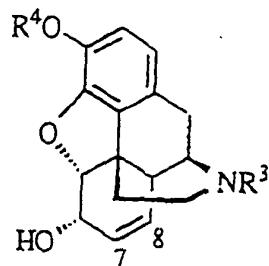
All of the previously disclosed methods have serious drawbacks for producing material to be used as a pharmaceutical drug. A desirable goal, met by the present invention, has been to devise a synthetic procedure without using commercially inaccessible and expensive reagents, and which cleanly produces the desired 4,5-Epoxymorphinan-6-oxyglucuronides, avoiding tedious and expensive purification steps.

## SUMMARY OF THE INVENTION

The present invention provides a commercially acceptable process for conjugation of 4,5-Epoxymorphinan-6-ols of formula [3] with Bromoglucuronides of formula [2] in the presence of Zinc containing compounds under conditions capable of forming 4,5-Epoxymorphinan-6-oxyglucuronides [1].



[2]

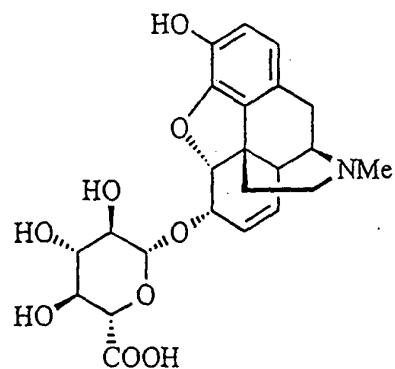


[3]

wherein

position 7 and 8 can be olefin as shown or dihydro adduct;  
R¹, R², R³, and R⁴, are as defined above.

This novel approach was used for the preparation of the known analgesic agent Morphine-6- $\beta$ -glucuronide [4] and of its  $\alpha$ -anomer.



[4]

Other features and advantages will be apparent from the specification and claims.

### DETAILED DESCRIPTION OF THE INVENTION

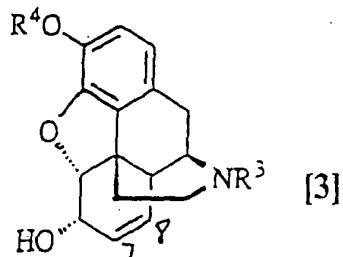
The present invention is related to a novel process for conjugation of 4,5-Epoxy morphinan-6-ols with Bromoglucuronides.

Particularly, the present invention relates to the use of Zinc containing compounds for the activation of Bromoglucuronides in the O-glycosylation reaction of 4,5-Epoxy morphinan-6-ols.

This novel approach has the following advantages:

- Zinc containing compounds as activating reagents of Bromoglucuronides are inexpensive and commercially available.
- Use of different O-protecting groups in the aglycon and in the Bromoglucuronide as well as different ratio of 4,5-Epoxy morphinan-6-ols and Zinc containing compounds enable to obtain high anomeric selectivity and produce at will with a high degree of preference either the  $\alpha$  or the  $\beta$  anomer.

Although any 4,5-Epoxy morphinan-6-ols are suitable for this O-glycosylation, preferably, compounds of formula [3] are used

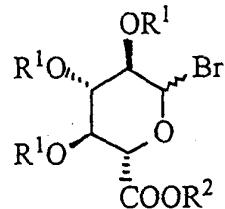


wherein

position 7 and 8 can be olefin as shown or dihydro adduct;  
 $R^3$  and  $R^4$  are as previously defined.

More preferably, said 4,5-Epoxy morphinan-6-ols are selected from 3-O-Acylmorphine, 3-O-Acynormorphine, 3-O-Acynalbuphine, 3-O-Acynalorphine, 3-O-Acyldihydromorphine, 3-O-Benzylmorphine, 3-O-Benzyl dihydromorphine, N,O<sup>3</sup>-Dibenzylnormorphine, Codeine, Ethylmorphine, Dihydrocodeine, Pholcodine, 3-O-Alkoxycarbonylmorphine, 3-O-Benzylloxycarbonylmorphine, N,O<sup>3</sup>-Bis(benzylloxycarbonyl)normorphine.

Although any Bromoglucuronide may be used, it is preferred that compounds of formula [2] are used.

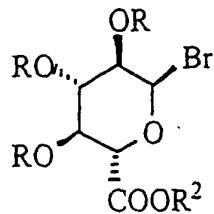


[2]

wherein

$R^1$  and  $R^2$  are as previously defined.

More preferably the Bromoglucuronides of the present invention are selected from the compounds of formula [2a].



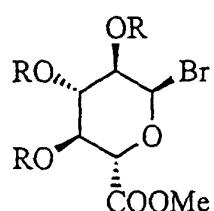
[2a]

wherein

R are acyl, alkoxy carbonyl, aralkoxy carbonyl, haloalkoxy carbonyl, vinyloxy carbonyl, allyloxy carbonyl;

R<sup>2</sup> is as previously defined.

Most preferably Bromoglucuronides of formula [2b] are used.



[2b]

wherein

R are as previously defined.

Although any Zinc containing compound suitable as activating reagents for this O-glycosylation can be used, preferably, Zinc Bromide is used.

It is preferred that about 0.01 equivalents to about 4 equivalents and especially preferred that about 0.5 equivalents to about 2 equivalents of Zinc containing compound is used.

Preferably about 1 equivalent to about 2 equivalents of the Bromoglucuronide [2] is used. It is specially preferred that about 1 equivalent to about 1.5 equivalents of Bromoglucuronide [2] is used. The said 4,5-Epoxy morphinan-6-ol [3] may be used as an individual compound or alternatively as corresponding salts thereof or complexes. Especially preferred is the use of said Zinc containing salt or complexes of [3] without using additional Zinc containing compounds as promoter for said coupling. It is preferred that the said complexes may be prepared *in situ*.

It may be also preferred to conduct the said Zinc activated O-glycosylation in the presence of additives to buffer or to promote the said Zinc containing compounds. The above additives may be selected from molecular sieves, tertiary amines, tetraalkylureas, organic and inorganic acids and salts.

Any reaction-inert solvent may be used. As used above and elsewhere herein, the expression "reaction-inert solvent" refers to a solvent which does not react or decompose with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product. In general, the solvent can comprise a single entity, or contain multiple components. Preferably the solvent is a non-protic reaction inert solvent and it is especially preferred that the solvent is Dichloromethane because of the excellent stereoselectivity it provides. Another solvent may be Chloroform or Dichloroethane.

Any environment or conditions (e.g. temperature, time, solvent) suitable for (i.e., capable of) forming the desired 4,5-Epoxymorphinan-6-oxyglucuronides may be used. However, it is preferred that the reaction occurs at a temperature of about - 20 °C to about 100 °C and preferably from about 40 °C to 65 °C. Below about - 20 °C the reaction can be slow and above about 100 °C undesired side reactions (e.g. anomerisation) can occur. This reaction is conveniently carried out at about 0.5 to about 3 atmospheres, however, the high pressures are especially preferred for the said coupling.

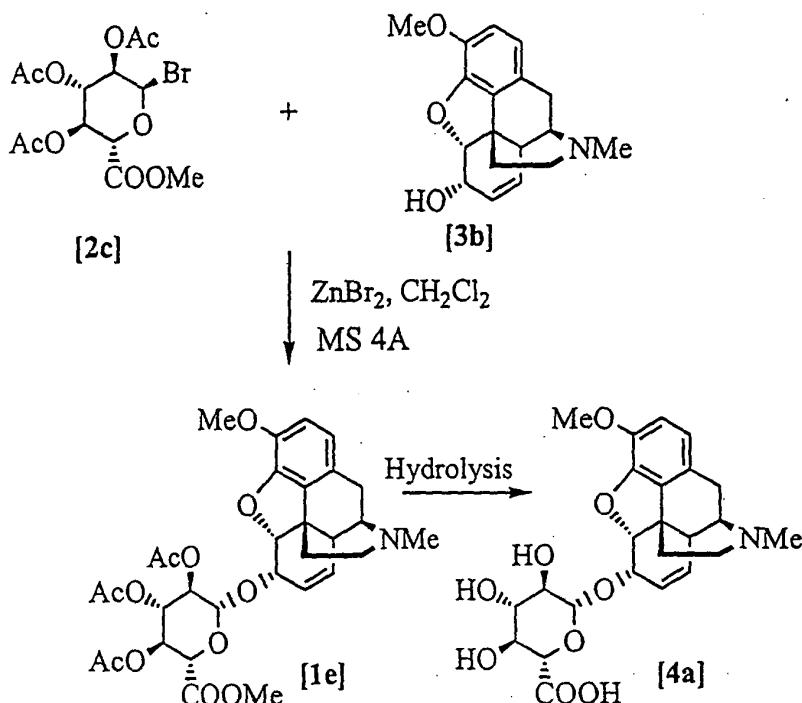
The present invention could be used as a general method to produce a large number of new compounds. As a result of the said coupling also the salts and complexes of 4,5-epoxymorphinan-6-oxyglucuronides [1] could be obtained in a convenient way.

This invention makes a significant advance in the field of 4,5-Epoxymorphinan-6-oxyglucosides by providing efficient methods of preparing both anomers of 4,5-Epoxymorphinan-6-oxyglucuronides. The deprotected end products are useful as analgesic agents.

It should be understood that the invention is not limited to the particular embodiments shown and described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

## Examples

### Example 1. Preparation of Codeine- $\beta$ -glucuronide [4a]



#### 1.1 Preparation of Methyl (3-O-methylmorphin-6-yl-2',3',4'-tri-O-acetyl- $\beta$ -D-glucopyranosid)uronate [1e]

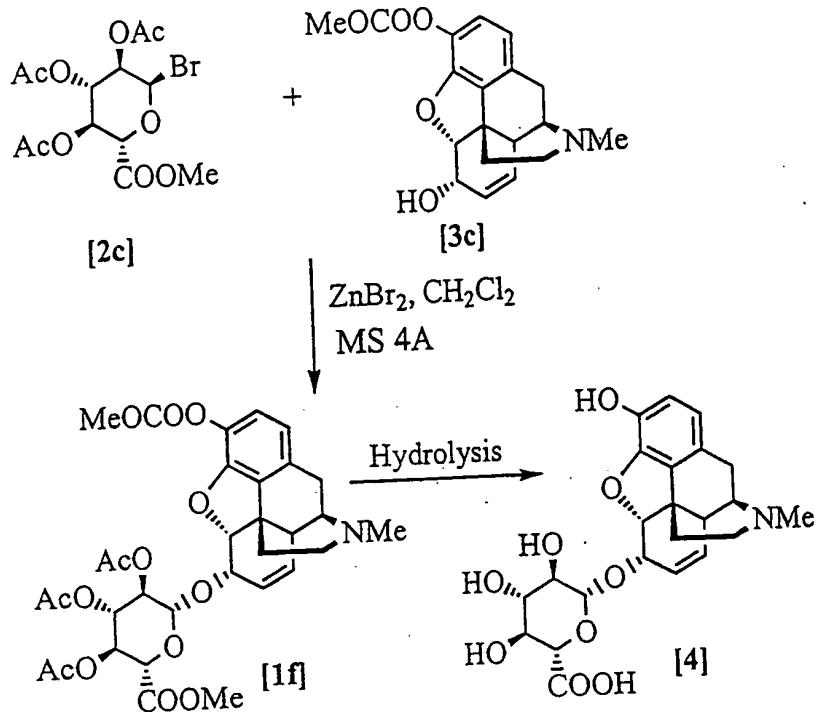
A mixture of Methyl acetobromo- $\alpha$ -D-glucuronate [2c] (0.20 g), Codeine [3b] (0.10 g), 3 $\text{\AA}$  Molecular Sieves (0.3 g) and Dichloromethane (10 mL) was stirred at room temperature for 5 hours. Anhydrous Zinc Bromide (0.08 g) was added in one portion and the resulting mixture was refluxed for 48 hours. Dichloromethane (20 mL) and Sodium Hydrogencarbonate saturated aqueous solution (10 mL) were added to the cooled reaction mixture. After stirring for 30 min the organic layer was separated and washed with Sodium

Hydrogencarbonate saturated aqueous solution and Water. The aqueous layers were combined and washed with Dichloromethane (20 mL). The combined organic layers were dried over anhydrous Sodium Sulfate, filtered and evaporated under reduced pressure. After purification of the residue the desired product was obtained in the yield of 58 % (0.12 g). Its structure was confirmed by  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )

### 1.2 Hydrolysis of compound [1e].

Hydrolysis of compound [1e] was carried out according to the known procedure (Carrupt, P.-A. et al., J. Med. Chem., 1991, v. 34, 1272). Codeine- $\beta$ -glucuronide was obtained with 50 % yield. Its structure was confirmed by  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ),  $^{13}\text{C}$  NMR, HR-MS.

**Example 2. Preparation of Morphine-6- $\beta$ -glucuronide [M6G]  
[4].**



**2.1 Preparation of Methyl (3-O-methoxycarbonylmorphin-6-yl-2',3',4'-tri-O-acetyl- $\beta$ -D-glucopyranosid)uronate [1f]**

A mixture of Methyl acetobromo- $\alpha$ -D-glucuronate [2c], (39.7 g, 100 mmol), 3-O-Methoxycarbonylmorphine [3c] (22.8 g, 66.5 mmol) 3 $\text{\AA}$  Molecular Sieves (50.0 g) and Chloroform (300 mL) was stirred at room temperature for 1 hour. Anhydrous Zinc Bromide (16.1 g, 71.4 mmol) was added in one portion and the resulting mixture was stirred at 50 - 55 °C for 60 hours under Argon. Sodium Hydrogencarbonate saturated aqueous solution (200 mL) was added to the cooled to room temperature reaction mixture and the stirring was continued for additional 30 min. The organic layer was separated, washed with water, dried over anhydrous Sodium Sulfate, filtered through a short

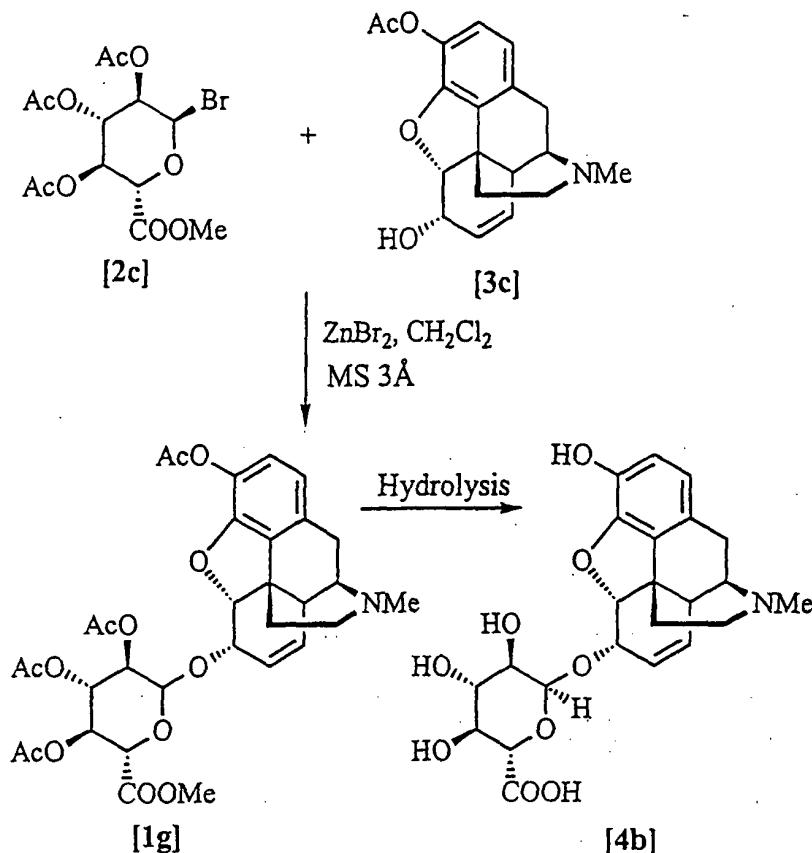
Silica gel column and evaporated under reduced pressure to give 35.0 g (80 %) of the crude product. After recrystallisation from iso-Propanol 20.3 g (46.4 % yield) of Methyl (3-O-methoxycarbonylmorphin-6-yl-2',3',4'-tri-O-acetyl- $\beta$ -D-glucopyranosid)uronate [1f] was obtained. Its structure was confirmed by  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ).

## 2.2. Hydrolysis of compound [1f]

Hydrolysis of compound [1f] was carried out according to known procedure (Carrupt, P.-A. et al., J. Med. Chem., 1991, v. 34, 1272) and gave M6G [4] with 56 % yield.

Its structure was confirmed by  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ),  $^{13}\text{C}$  NMR.

## Example 3. Preparation of Morphine-6- $\alpha$ -glucuronide [4b].



### 3.1 Preparation of Methyl (3-O-acetylmorphin-6-yl-2',3',4'-tri-O-acetyl- $\alpha$ / $\beta$ -D-glucopyranosid)uronate [1g]

A mixture of Methyl acetobromo- $\alpha$ -D-glucuronate [2c] (6.0 g, 15 mmol), 3-O-Acetyl morphine [3c] (3.23 g, 10 mmol) and  $3\text{\AA}$  Molecular Sieves (9.0 g) and Dichloromethane (50 mL) was stirred at room temperature for 5 hours. Anhydrous Zinc Bromide (4.50 g, 20 mmol) was added in one portion and the resulting mixture was refluxed for 48 hours. Solution of Sodium hydrogencarbonate (8.0 g) in 80 mL water and Dichloromethane (80 mL) were added to the cold solution. After stirring for 30 min the organic layer was separated and the aqueous layer was washed with Dichloromethane. The combined organic solution was washed with water, dried over anhydrous Sodium Sulfate, filtered and evaporated under reduced pressure. The residue was

purified on a short Silica gel column (Dichloromethane → Dichloromethane/Methanol 30 : 1 v/v) and after concentration under reduced pressure 5.7 g of yellowish powder of the desired Methyl(3-O-acetylmorphin-6-yl-2',3',4'-tri-O-acetyl-D-glucopyranosid)uronate [1g] ( $\alpha/\beta$  6:1 mixture according to  $^1\text{H}$  NMR spectra) (91 % yield) was obtained.

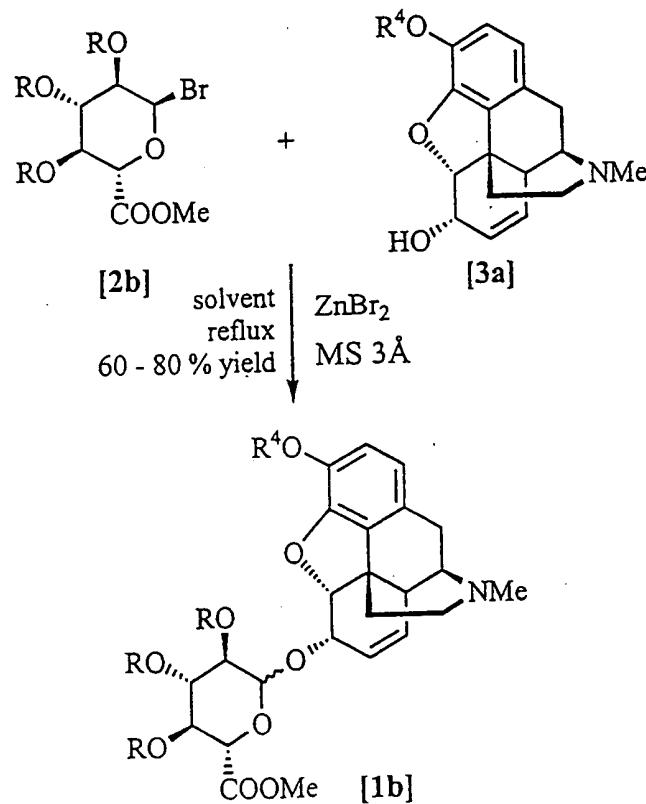
### 3.2 Hydrolysis of compound [1g].

Sodium Hydroxide (0.40 g, 10.0 mmol) solution in 7.5 mL water was added to a stirred solution of Methyl (3-O-acetylmorphin-6-yl-2',3',4'-Tri-O-acetyl- $\alpha/\beta$ -D-glucopyranosid)uronate (1.6 g, 2.0 mmol) in 30 mL Methanol and the mixture was stirred overnight at room temperature. The solution was then acidified with glacial Acetic acid (5.25 g, 87.3 mmol) to pH 5.5. The solution was cooled to 0 °C, Ethanol (20 mL) was added and the obtained mixture was stirred for 1.5 hours. The white precipitate formed under these conditions was filtered off and washed with Ethanol (2 mL). After drying under reduced pressure at 80 °C 0.63 g (62 % yield) of Morphine-6- $\alpha$ -glucuronide [4b] was obtained. Its structure was confirmed by  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ),  $^{13}\text{C}$  NMR, HR-MS.

**Example 4-20. Preparation of compound of formula [1b]**

The syntheses are described by the following Scheme.

The procedures set forth in Example 3 were followed with the exceptions apparent from Table 1. Ratio  $\beta/\alpha$  was determined according to  $^1\text{H}$  NMR and/or HPLC.

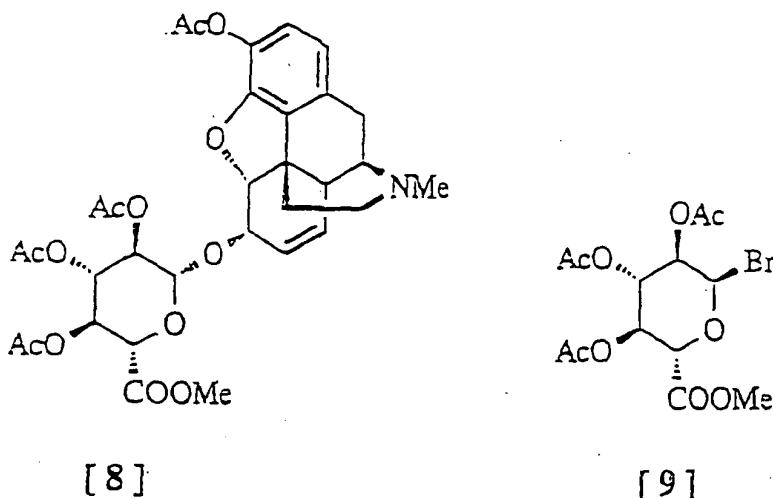


The procedures set forth in Example 3 were followed with the exceptions apparent from Table 1. Ratio  $\beta/\alpha$  was determined according to  $^1\text{H}$  NMR and/or HPLC.

Table 1

Ex. No.	R <sup>4</sup>	R	ZnBr <sub>2</sub> / [3a]	Solv.	β / α
4	Ac	Ac	0.8	CH <sub>2</sub> Cl <sub>2</sub>	10:1
5	Ac	Ac	0.9	CH <sub>2</sub> Cl <sub>2</sub>	6:1
6	Ac	Ac	1.0	CH <sub>2</sub> Cl <sub>2</sub>	2:1
7	Ac	Ac	1.2	CH <sub>2</sub> Cl <sub>2</sub>	1:2
8	Ac	Ac	1.5	CH <sub>2</sub> Cl <sub>2</sub>	1:4
9	Ac	Ac	>1.5	CH <sub>2</sub> Cl <sub>2</sub>	1:6
10	Ac	i-Bu	0.90	CH <sub>2</sub> Cl <sub>2</sub>	2:1
11	Ac	i-Bu	1.2	CH <sub>2</sub> Cl <sub>2</sub>	1:1
12	i-Bu	i-Bu	0.85	CH <sub>2</sub> Cl <sub>2</sub>	3.5:1
13	i-Bu	i-Bu	1.0	CH <sub>2</sub> Cl <sub>2</sub>	2:1
14	Bz	Ac	1.0	CH <sub>2</sub> Cl <sub>2</sub>	2:1
15	Bz	i-Bu	0.9	CH <sub>2</sub> Cl <sub>2</sub>	29:1
16	Bz	i-Bu	1.5	CH <sub>2</sub> Cl <sub>2</sub>	6:1
17	Bz	Bz	1.0	CH <sub>2</sub> Cl <sub>2</sub>	10:1
18	MeOCO	Ac	1.0	CHCl <sub>3</sub>	6:1
19	MeOCO	Ac	1.4	CH <sub>2</sub> Cl <sub>2</sub>	5:1
20	Me	Ac	1.1	CH <sub>2</sub> Cl <sub>2</sub>	>99:1

**Example 21. Preparation of Methyl (3-O-Acetylmorphin-6-yl-2',3',4'-Tri-O-acetyl-β-D-glucopyranosid)uronate of formula [ 8 ]**



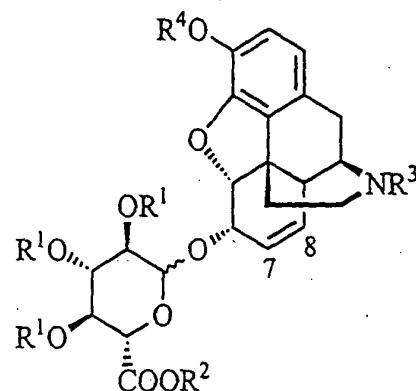
A suspension of 6.00 g of Methyl Tri-O-acetyl-1- $\alpha$ -bromo-1-deoxy-D-glucopyranuronate of formula [ 9 ], 3.23 g of freshly prepared, vacuum-dried 3-O-Acetyl morphine<sup>6</sup> and 9.00 g of 3 $\text{\AA}$  Molecular Sieves in CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 5 hours. Anhydrous Zinc Bromide, 2.20 g was added in one portion and the resulting mixture was refluxed for 24 hours. Then an additional 0.30 g of anhydrous Zinc Bromide was added and the mixture was refluxed for additional 24 hours. After this period, the red solution was cooled to room temperature and the mixture of Methylene Chloride (150 mL) and Sodium Hydrogen carbonate saturated aqueous solution (80 mL) was added to the reaction mixture. After stirring for 30 min. the organic layer was separated and washed consequently with Sodium Hydrogen carbonate saturated aqueous solution and Water. The combined aqueous layers were washed with Methylene Chloride. The combined organic layers were dried over Sodium Sulphate anhydrous, filtered and evaporated under reduced pressure. After purification of the residue the desired product was obtained in the yield of 91 % (5.7 g).

*References:*

1. Osborne, R., et al., Br. J. Clin. Pharm. 1992, v. 34, 130
2. Frances, B., et al., J. Pharm. Exp. Ther., 1992, v. 262, 25

## Claims

1. A process for the synthesis of a protected 4,5-Epoxy morphinan-6-oxyglucuronide of formula [1] or a salt or complex thereof



[1]

wherein:

position 7 and 8 are olefin as shown or dihydro adduct;

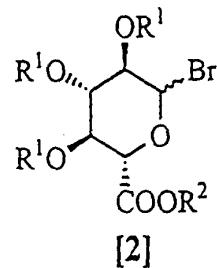
R<sup>1</sup> is alkyl, haloalkyl, arylmethyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, haloalkoxycarbonyl, vinyloxycarbonyl or allyloxycarbonyl,

R<sup>2</sup> is alkyl, haloalkyl or aralkyl;

R<sup>3</sup> is alkyl, arylmethyl, allyl, cyclopropylmethyl, cyclobutylmethyl, hydrogen, acyl, alkoxycarbonyl, aralkoxycarbonyl, haloalkoxycarbonyl, vinyloxycarbonyl or allyloxycarbonyl;

R<sup>4</sup> is alkyl, haloalkyl, arylmethyl, 2-(4-morpholinyl)ethyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, haloalkoxycarbonyl, vinyloxycarbonyl or allyloxycarbonyl.

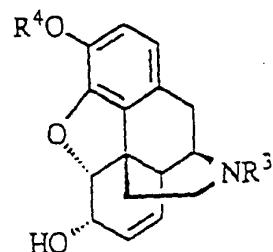
comprising reaction of a Bromoglucuronide of the formula [2]



wherein

R¹ and R² are as previously defined;

with a 4,5-Epoxy morphinan-6-ols of the formula [3] or a salt or complex thereof



[3]

wherein

R³ and R⁴ are as previously defined;

in the presence of a Zinc containing compound under conditions capable of forming said protected 4,5-Epoxy morphinan-6-oxyglucuronide [1] or a salt or complex thereof.